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Thrombotic Thrombocytopenic Purpura—Hemolytic Uremic Syndrome (TTP-HUS) Following Treatment with Deoxycoformycin in a Patient with Cutaneous T-Cell Lymphoma (Sezary Syndrome): A Case Report

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We present a case of a patient who developed all manifestations of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) acutely following treatment of cutaneous T-cell lymphoma (CTCL, Sezary syndrome) with deoxycoformycin (pentostatin). Symptoms and signs included severe thrombocytopenia and microangiopathic hemolytic anemia; hallucinations, confusion and disorientation; oliguric acute renal failure requiring hemodialysis; and fever. No other etiology for these symptoms and signs was present. Complete recovery followed treatment for one month with plasma exchange and glucocorticoids. During the succeeding 20 months she has remained well and her CTCL remains stable on no further treatment. This case and two previously published cases suggest that acute and severe TTP-HUS may be a dose-dependent toxicity of deoxycoformycin (pentostatin). Am. J. Hematol. 61:268–270, 1999. © 1999 Wiley-Liss, Inc.

Key words: thrombotic thrombocytopenic purpura; hemolytic uremic syndrome; TTP-HUS; deoxycoformycin, pentostatin

INTRODUCTION

Deoxycoformycin (DCF, pentostatin) is an analogue of the purine adenosine and a potent inhibitor of adenosine deaminase, an enzyme critical for lymphoid development. It is effective therapy for Sezary syndrome and T-cell prolymphocytic leukemia [1]. There are two case reports of DCF-associated hemolytic-uremic syndrome [2,3]. Our patient developed a life-threatening illness with all manifestations of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) abruptly following treatment with DCF and recovered completely following plasma exchange treatment.

CASE REPORT

C.W. is a 48-year-old white female whose complication of DCF was in April, 1997. She had a history of intermittent, generalized pruritis with erythema since July, 1991 which was diagnosed as cutaneous T-cell lymphoma (CTCL) by lymph node and skin biopsies on July 11, 1996. Physical examination at that time was unremarkable except for an erythematous rash on her trunk; no plaques or nodules were present. There was no palpable lymphadenopathy, hepatomegaly, or splenomegaly; computed tomography demonstrated only lymphadenopathy in the inguinal and axillary regions. Peripheral blood smear demonstrated Sezary cells with confirmation of monoclonal T cells by flow cytometry. She was treated with photopheresis beginning in September 1996 with resolution of her lymphadenopathy, but her erythrodermic rash progressed to involve her face, neck, and extremities. Alpha interferon (5 million units/day) and isotretinoin were added to photopheresis on February 3, 1997 but there was no improvement of her skin involvement or Sezary cell count. Photopheresis was discontinued on March 19; interferon and isotretinoin were discontinued after April 13. Because of persistent active

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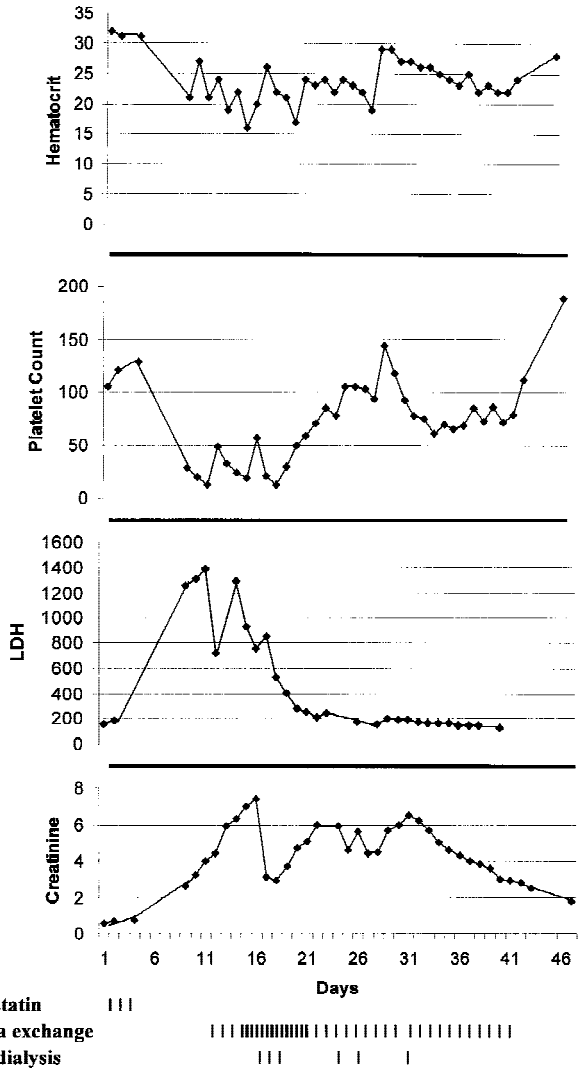

Fig. 1. Clinical course of patient C.W. Day 1 is April 15, 1997, the day the three day course of deoxycoformycin was begun. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome was suspected and daily plasma exchange begun on day 11 (April 24), was performed twice daily for 7 days (heavy bars, days 14–20), and then continued daily until day 41 except for skipping day 30. Platelet transfusions were given on days 11 and 15. Six hemodialysis treatments were required between days 16 and 31. Units for data are hematocrit (%), platelet count (cells × 10^3/μl), LDH (U/l), creatinine (mg/dl).

CTCL, she was treated with DCF at 5 mg/m^2 for three consecutive days, April 15–17. On April 18 she began to feel ill with abdominal cramps, nausea, and vomiting. On April 19 and 20 she developed abdominal pain with chills and fever to 101°F. On April 20 her urine volume decreased. She was admitted to the hospital on April 22 with a hematocrit of 21%, platelet count of 28,000/μl, LDH of 1253 U/l, and creatinine of 2.6 mg/dl. Laboratory data are presented in Figure 1. The initial impression was sepsis, even though her white blood count cell count was 5700/μl with 58% neutrophils, and antibiotic treatment was begun. However no infectious etiology was identified. TTP-HUS was suspected and plasma exchange treatment using fresh frozen plasma [4] begun on April 24 when she had severe thrombocytopenia, hemolytic anemia with severe red cell fragmentation and a negative direct antiglobulin test, acute oliguric renal failure, and fever. Neurologic abnormalities developed on April 27 manifested by disorientation with visual and auditory hallucinations. Cerebrospinal fluid examination was normal. On April 27, because of worsening of all features of TTP-HUS, plasma exchange was increased to twice daily for seven days, methylprednisolone (100 mg/day) was added, and hemodialysis was required. With this regimen, her hematologic and neurologic status gradually improved, though her personality changes did not completely resolve until May 20. Hemodialysis was required until May 14. Plasma exchange was discontinued on May 24 after 37 treatments even though she remained thrombocytopenic. Marrow biopsy on May 23 was normal except for mild hypocellularity. Her platelet count recovered to normal on May 30. She has remained active, her CTCL has remained stable, and her laboratory data have remained normal (with the exception of Sezary cells) on no further treatment to the present time (January, 1999).

DISCUSSION

Among the diverse etiologies for the syndrome of TTP-HUS, adverse reactions to drugs are recognized with increasing frequency. Drug-induced TTP-HUS may be immunologically-mediated, as with quinine [5] and possibly also ticlopidine [6], or a dose-related toxicity, as with mitomycin C [7]. Two previous patients with clinical syndromes similar to TTP-HUS following DCF have been reported [2,3]. The first patient, a 39-year-old man with T-cell lymphoma, developed acute renal failure on the third day of a 5-day regimen of DCF (5 mg/m^2/day); renal biopsy demonstrated thrombotic microangiopathy [2]. There were no neurologic abnormalities, no hemolysis, and his platelet count remained greater than 100,000/μl. The patient recovered in 3 weeks with hemodialysis. The second patient, a 56-year-old woman with T-cell leukemia, developed severe thrombocytopenia, microangiopathic hemolytic anemia, and renal failure immediately following the administration of DCF (5 mg/m^2/day for 3 days) [3]. Response to treatment with plasma infusions, heparin, vincristine, and dipyridamole was incomplete and the patient died with cytomegalovirus pneumonia seven weeks later. No neurologic abnormalities occurred until late in her course, when a seizure occurred in association with severe hypertension.

Our patient had all of the acute and severe manifestations of TTP-HUS promptly following administration of

similar aggressive dose of DCF for refractory Sezary syndrome. The lack of prior exposure to DCF in any of these three patients and the greater than standard doses suggest a direct toxicity. DCF at a dose of 4 mg/m^2/week for 4 weeks, then every 2 weeks, had no major renal or neurologic toxicities in 145 patients [1]. However both renal and neurologic toxicities have been described at higher doses. At a dose of 10 mg/m^2 for 5 days, 12 of 44 patients (27%) had acute renal failure; anuria with acute tubular necrosis occurred in 6 patients [8]. Dose-dependent neurotoxicity occurs at 5–30 mg/m^2 for 3 days, with up to 60% of patients at the higher doses having somnolence, seizures, or coma [9].

This experience suggests that acute and severe but reversible TTP-HUS is a toxicity of deoxycoformycin.

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